REMARKS

Claims 1 and 6-8 are currently pending in the application. Claims 1 and 6-8 are in independent form. The claims have been amended to recite that the administration of the therapeutic compound occurs post ischemic event. Support for these amendments can be found throughout the specification and examples, especially on page 6: "the purpose of the present invention is to promote an improved outcome from ischemic cerebral injury..." (lines 8-10), "...administration promotes functional improvement after stroke, injury, aging, and degenerative disease" (lines 14-15), and "nitric oxide administered at propitious times after CNS injury promotes neurogenesis in the brain..." (lines 19-20). Also, in each example provided in the specification, the therapeutic compound was administered after causing occlusion to the MCA in rats. In other words, administration occurs only after stroke or injury to the brain, i.e. after an ischemic event has occurred.

Applicants wish to express their appreciation for the courtesies extended Applicants' representative, Kenneth I. Kohn, during a personal interview conducted on July 10, 2007. During the interview the cited prior art was discussed and agreement was reached that the prior art does not teach administration of the therapeutic compounds recited in the presently pending claims post stroke.

Claims 1 and 9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Cooke, et al. patent. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Cooke, et al. patent is respectfully requested.

The Office Action has held that the Cooke, et al. patent teaches administering L-arginine in a vascular injury, with emphasis on atherogenesis. The Office Action has concluded that one of ordinary skill in the art would be motivated to administer L-arginine to patient, post stroke, in order to promote neurogenesis or growth of new neurons because L-arginine is the substrate for nitric oxide production and has been shown to induce an endothelium-dependent increase in cerebral blood flow in humans.

However, when read more specifically, the Cooke, et al. patent merely discloses methods for limiting the occurrence or progression of atherosclerosis and restenosis or a method of increasing the blood flow to areas with decreased blood

flow. There is no disclosure for the regeneration of neurons as is disclosed in the presently pending independent claims. Cooke, et al. discloses the prophylactic use of compounds to maintain an enhanced level of nitric oxide in the vessel wall (col. 3, line 65 – col. 4, line 3), or where atherosclerosis is "suspected", administration can begin at any time (col. 4, lines 55-57). There is no indication that this administration can be after an ischemic event and there is further no evidence of an essential step of the presently pending claims of augmenting new neural growth or increasing neurological function. The method disclosed in the Cooke, et al. patent has little to no applicability to the method recited in the presently pending independent claims.

In contradistinction, the presently pending independent claims claim therapeutic compounds including PDE5 inhibitors and related compounds, for inducing brain remodeling and restoring neurological function, completely independent of the effect of NO donors on the volume of infarction. As disclosed throughout the currently pending patent application and specifically claimed, the functional benefit is derived from treatment under conditions in which the volume of brain damage is unaltered by the treatment. Further, the claimed methods are used to treat and remodel viable brain. The method activates endogenous restorative mechanisms within the non-injured tissue, so as to compensate for the damage, and thereby to enhance neurological function. The therapy is designed to be given days and weeks after the injury, i.e. post ischemic event, and the neurogenesis is totally independent of any affect of treatment of the lesion. The claimed method is specifically delayed until the completion of infarction, and can even be administered 24 or more hours after stroke. The neurogenesis occurs as stated on page 7, lines 5-15 due to increased levels of cGMP resulting from the administration of the NO donor. The increased amount of cGMP increases the number of progenitor cells and the number of Tuj1 immunoreactive cells in the ischemic brain, thus enhancing the functional recovery after stroke. The recovery includes the increase of parenchymal cells as a result of the proliferation of new neurons, therefore, the parenchymal cells are increased as a result of the neurogenesis. cGMP functions to increase neurons. Additionally, the methodology disclosed in the Cooke, et al. patent does not initiate neurogenesis. It is actually contrary to the common knowledge of those in skill in the

art to have administered any compounds after the completion of the stroke. Instead, it was believed by those of skill in the art that upon completion of the stroke, an individual was no longer able to be treated and must instead learn to survive with the results of the stroke. Since the Cooke, et al. patent does not disclose or suggest the method and compound of the presently pending independent claims, the claims are patentable over the Cooke, et al. patent, and reconsideration of the rejection is respectfully requested.

Claims 1, 6-12 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Cooke, et al. patent taken with the Liao patent in view of the Kaposzta, et al. reference taken with the Ohtsuka, et al. reference. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Cooke, et al. patent taken with the Liao, patent in view of the Kaposzta, et al. reference taken with the Ohtsuka, et al. reference is respectfully requested.

As referenced above, the Cooke, et al. patent neither discloses nor suggests the invention as recited in the presently pending independent claims.

The Office Action has held that the Liao patent teaches a surprising connection was made in connection with the treatment of ischemic stroke, wherein brain injury reduction is measured by determining a reduction in the infarct size in treated versus control groups. At column 8, lines 62-65 there is further disclosed that the "brain injury reduction, as demonstrated in the examples below, can be measured by determining a reduction in infarct size in the treated versus the control groups." In other words, the treatment is similar to that of the Moskowitz patent previously cited in the present application, which does not provide the same results as accomplished by the method of the presently pending claims.

As was found with regard to the Moskowitz patent, the Liao patent merely discloses that stroke can be treated during a finite period of time. It is commonly known to those of skill in the art that there is a distinct period of time in which the damage occurring from a stroke can be mediated. Subsequent to this time period, it was believed that treatment was futile. The Liao patent discloses at column 9, lines 21-30 that the treatment can either be prophylactic or can be acute. The acute treatment is defined as "at the onset of symptoms of the condition or at the onset of

a substantial change in the symptoms of an existing condition." This definition is commensurate in scope with the knowledge of those of skill in the art defined above. Essentially, the Liao patent discloses treatment before or during the stroke itself. While Liao states that "the invention ... is useful for treating subjects with hypoxia-induced conditions", there is no reason to interpret this statement to mean that treatment is given after stroke as it must be read in the context of the whole patent disclosure (col. 3, lines 45-46). While conditions caused by hypoxia can be treated, this treatment is given prior to any hypoxia-induced event. There is no indication from the Liao patent that treatment can be given post ischemic event. Every example given by Liao is directed to prophylactic treatment before ischemia occurs, especially in Example 17 (simvastatin treatment for 14 days followed by production of cerebral ischemia).

As discussed during the personal interview, to further provide evidence that Liao only discloses prophylactic treatment or at most treatment during a stroke, Applicant submits herein a journal article by Liao (proc. Natl. Sci. USA, Vol. 95, pp. 8880-8885, July 1998). This article also examines the effect of HMG-CoA reductase inhibiting drugs on ischemia through their mechanism of up-regulating endothelial nitric oxide synthase. The goal of the article is "to determine whether statin administration confers protection against ischemic stroke" and therefore simvastatin was administered daily for 14 days to mice before MCA occlusion (p. 8881). Further, the authors state that "the major finding in this study is that prophylactic treatment with HMG-CoA reductase inhibitors protects against ischemic strokes after focal brain ischemia" (p. 8884). This article teaches much of the same methods and findings with simvastatin as the Liao patent. Accordingly, there is no motivation for treatment after the stroke is complete, i.e. post ischemic event, since this is a point in time substantially after the onset of the symptoms.

Finally, with regard to the Kaposta, et al. and Ohtsuka, et al. references, these references merely disclose use of compounds prophylactically. There is no disclosure for the use of the compounds post ischemic event for creating neurogenesis. Since none of the cited references alone or in combination with one another suggest the currently claimed invention, it is respectfully submitted that the

claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not discussed above are ultimately dependent upon at least one of the independent claims discussed above. No prior art reference makes up for the deficiencies of that reference as applied against the independent claims as no prior art reference discloses or suggests the invention as set forth in the claims as discussed in detail above.

It is respectfully requested that the present amendment be entered in order to place the application in condition for allowance or at least in better condition for appeal. The application is placed in condition for allowance as it addresses and resolves each and every issue that remains pending. The claims have also been amended to clearly distinguish them over the prior art. The claims have not been made broader in scope, thereby requiring no further searching nor raise any new issues. In fact, all claims now include limitations of previously pending claims and were therefore previously searched. The application is made at least in better condition for appeal as the amendment removes any issues thereby simplifying the issues on appeal. That is, each and every rejection has been overcome. Hence, it is respectfully requested that the amendment be entered.

Applicants respectfully request to be contacted by telephone if any remaining issues exist.

In summary, the presently claimed invention is in condition for allowance, which allowance is respectfully requested. If any remaining issues exist, Applicants respectfully request to be contacted by telephone at (248) 539-5050.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Dated: July 17, 2007

CERTIFICATE OF ELECTRONIC FILING VIA EFS-WEB

Date of Electronic Filing: 7-17-07

I hereby certify that this correspondence is being electronically filed with the United States Patent & trademark Office on the above date.

Connie Herty